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## Key Considerations for Second-Line PBC Treatment

### Announcer:

You're listening to *GI Insights* on ReachMD, and this episode is sponsored by Gilead Sciences, Inc. Here's your host, Dr. Charles Turck.

### Dr. Turck:

This is *GI Insights* on ReachMD and I'm Dr. Charles Turck. Today, I'm joined by Dr. Sammy Saab and David Bernstein to discuss the transition from first- to second-line therapies for primary biliary cholangitis, or PBC for short. Dr. Saab is a Professor in the Departments of Medicine and Surgery at UCLA's David Geffen School of Medicine and an Adjunct Professor of Nursing at the UCLA School of Nursing. Dr. Saab, welcome to the program.

### Dr. Saab:

Oh, thank you for having me. I'm very excited to talk about this very timely topic.

### Dr. Turck:

Also joining us is Dr. Bernstein, who's a Professor of Medicine at NYU's Grossman School of Medicine and the Director of Gastroenterology and Ambulatory Services at NYU Langone Health. Dr. Bernstein, it's great to have you with us as well.

### Dr. Bernstein:

Thank you very much for having me.

### Dr. Turck:

So let's start with you, Dr. Saab. What's the current standard of care after patients receive a PBC diagnosis?

### Dr. Saab:

So primary biliary cholangitis, or PBC, is associated with both hepatic and extrahepatic manifestations. The liver ones include cirrhosis and liver failure. Indeed, before we had any therapy, PBC was a leading indication for liver transplant in the United States and across the globe. Today, the standard of care for newly diagnosed patients of PBC is ursodeoxycholic acid. This is given a dose of 13 to 15 mg per kg in two divided doses per day. Now, alkaline phosphatase is an enzyme that is an important predictor of non-new liver-related outcomes, but it's a barometer of treatment efficacy. The natural history of PBC is directly related to decreases in this enzyme, alkaline phosphatase, with therapy.

Ursodeoxycholic acid is effective in improving alkaline phosphatase in most patients. Approximately 60 percent of treated individuals will respond to therapy, so approximately 60 percent of individuals respond to ursodeoxycholic acid, but that leaves us 40 percent who do not respond to first-line therapy.

### Dr. Turck:

And turning to you now, Dr. Bernstein, how can we evaluate a patient's response to first-line therapy?

### Dr. Bernstein:

So, great question. We make an assessment of response to the first-line therapy based upon biochemical parameters. So, at six months after starting treatment, we look at three parameters: the alkaline phosphatase and the importance of bringing that down to less than 1.67 times the upper limit of normal; decreasing the alkaline phosphatase, in addition, by at least 15 percent; and maintaining the bilirubin, normal or decreasing it to below the limit of normal. So, we look at alkaline phosphatase and bilirubin.

What's exciting, or interesting, is that our parameters are changing. So, we have learned that in certain patients, in particular those with

advanced fibrosis and/or less than 62 years of age, we really want to bring the alkaline phosphatase taste down to normal. And so, again, what do we look at? At six months on urso, we make an assessment as to whether or not it's working. The key point is the alkaline phosphatase should come down to at least 1.67 times the upper limit of normal, probably more than that, and the bilirubin should remain normal or go down.

**Dr. Turck:**

Well, with that mind, Dr. Saab, what are the criteria for selecting candidates for second-line therapy? Who makes a good candidate?

**Dr. Saab:**

Second-line therapies are considered for two major reasons. One is lack of efficacy, and those 40 percent of individuals who don't respond to ursodeoxycholic acid, and a small subset that have adverse reactions to ursodeoxycholic acid.

There's also a time variable. The need for assessment in regards to treatment response is moved according to the severity of liver disease. In those patients with PBC that have mild liver disease, an assessment could generally be done around 12 months after starting treatment. But those with more advanced liver disease, their window is more narrow, and we should assess the response by six months.

**Dr. Turck:**

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Sammy Saab and David Bernstein about key considerations for transitioning primary biliary cholangitis patients to second-line therapies.

So, now that we have some background on the first steps for transitioning patients to second-line therapies, let's zero in on available options. Dr. Bernstein, would you share the clinical trial data on the efficacy and safety of emerging second-line treatments?

**Dr. Bernstein:**

Sure. And this is actually an exciting year for PBC because we have two new therapies which were approved—both in 2024. The first that was approved is elafibranor, which is a PPAR alpha and delta agonist. And in the ELATIVE trial, which was published in *New England Journal* also this year, it looked at response rates of patients who were taking elafibranor plus urso versus urso alone, and the endpoint was a composite endpoint: a decrease in alkaline phosphatase to less than 1.67 times the upper limit of normal, a decrease in alkaline phosphatase by 15 percent, and a bilirubin which remained normal. And so I'm going to refer to that as a composite endpoint because it's the easiest.

In that, 51 percent of the patients who are on the combination therapy reached that endpoint. Seventy-one percent of the patients whose alkaline phosphatase was less than three times the upper limit of normal at baseline in the study brought their alkaline phosphatase down and reached the composite endpoint, and 15 percent of the patients actually normalized the alkaline phos. There was an improvement in pruritis itching, which is an important aspect of the treatment of PBC. But it didn't reach statistical significance and the drug was safe. But there was an increased incidence of bone fracture in patients who received this medication compared to placebo. Unclear why that is. Several of the patients fell or were in a motor vehicle accident, and just in general, patients with PBC are at a higher risk of fractures related to osteoporosis. So, that's elafibranor.

If we move over to the second drug which is approved, which is seladelpar, that's a PPAR delta agonist given at a dose of 10 milligrams once a day. And in the RESPONSE trial, which was also published in 2024, it used the same composite endpoint as the elafibranor study, so I'm not going to repeat that.

But 61 percent of the patients who received the seladelpar with urso met the composite endpoint. And there was a significant improvement in pruritis, so that's important. In addition, 25 percent of the patients who were treated with seladelpar normalized their alkaline phosphatase. And earlier, we mentioned the importance of normalization of alkaline phosphatase, especially in those patients with advanced fibrosis. In this study, there was also an increased risk of fracture in the patients who received the seladelpar. So, both studies, about the same.

So if you put both clinical trials together, we've made significant advances in the treatment of these patients who were refractory or didn't respond to ursodeoxycholic acid and it's really an exciting time since the drugs are easy to use and safe.

**Dr. Turck:**

Given those treatment options, Dr. Saab, how can we select an approach and optimize the patient's experience when transitioning between the first and second-line therapies?

**Dr. Saab:**

Changing gears during any therapy is a source of anxiety, and it's difficult for the patient. It's important to work as a team with the patient

who needs second-line therapy. It's essential that we highlight the goals of therapy and stress the importance of decreasing or even normalizing alkaline phosphatase. Also important to discuss efficacy and safety of second-line therapy and make sure the patient knows that our team is always available if any of the uncommon adverse effects should occur with second-line therapy. Response and potential adverse effects with second-line therapy could be assessed between 1 and 3 months after starting second-line treatment.

**Dr. Turck:**

We've certainly covered a lot today, but as we approach the end of our program, Dr. Bernstein, are there any final takeaways you'd like to leave with our audience?

**Dr. Bernstein:**

So, I think there are a couple that are important in this disease. First and foremost, I think, is that PBC, or primary biliary cholangitis, is uncommon but not rare, and it's out there, and so it's important to recognize it and to evaluate patients who are appropriate – those with elevated alkaline phosphatase – for this condition.

The second is, it's an exciting time since with ursodeoxycholic acid, 60 percent of the patients have an adequate response. Now, we have therapies where 60 to 70 percent of the people who failed will have a response. The number of people who don't have a response are far lower, so we've made significant progress.

Third thing is when we treat this disease, we treat histologic progression, so what's going on within the liver, and we also treat its symptoms. And although we didn't discuss the treatment of pruritis, which is a main concern in patients with PBC, there's a lot of new therapies being evaluated for that, and so it's important to remember that as well. We treat the disease, and we treat the symptoms.

And last but not least is that our endpoints are changing. So where we used to think everyone had to get below 1.67 times the upper limit of normal, a really difficult number to remember, we're now really pushing that down. And it looks as though it would probably be best for most patients simply saying, the lower you can get the alkaline phosphatase towards normal, the better the long-term prognosis.

**Dr. Turck:**

Well, with those key take-home points in mind, I want to thank my guests, Dr. Sammy Saab and David Bernstein, for joining me to discuss how we can support patients with primary biliary cholangitis as they transition to second-line therapies. Dr. Saab, Dr. Bernstein, it was great having you both on the program.

**Dr. Saab:**

Well, thank you for having me. It was a pleasure to be here talking about this very important topic, and it's heartwarming to know that we have second-line therapies for our patients.

**Dr. Bernstein:**

Thank you so much for allowing me to come onto this. I enjoyed it as well.

**Announcer:**

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